number of the points raised by the Examiner, and more clearly set forth applicant's method, according to a basic aspect of which a sample is prepared and tested producing a multi-dimensional data output, a distribution. New dependent claims 23-25 are added, directed to preferred aspects of applicant's testing distribution invention.

As now set forth in claim 1, applicant's invention includes a testing method wherein a sample is taken of a food product, the sample is subjected to a preparation process (e.g., to release and present sequences) and to a testing procedure that simultaneously tests for a plurality of different sequences of each of plural different organisms or species that are potentially present in the sample. The testing, rather than producing a binary output (such as present/absent or good/bad) for each of a set of pathogens, produces a data object - a distribution. The distributions are multi-dimensional measurement data objects, and have many new and advantageous properties that may be analogized, for example, to spectra. These are applied in further aspects of the system to form specialized informatics and database systems.

As described in the disclosure, selection of the specific target sequences for each of the organisms (which is done before fabrication of the probes, or in multiple stages during optimization of the set) may be carried out not simply to detect the presence or absence of a particular species, but to quantify the amount of a species present, or identify particular strains (and not just the species) that are present (page 17, first full paragraph.) This aspect - the multi-dimensionality of distributions brings great power in the present invention. According to further aspects of the invention, these data objects are organized in a database that may include entirely disparate data (e.g., invoice source, harvest time or crop location and weather data, or process parameters). Furthermore, additional steps of the method apply data mining, correlation or other database processing to recognize connections and/or effect actions related to a wide range of technical concerns, such as culture, transportation, processing and taste or texture of food components. These other aspects may involve physical or physical/historical data (e.g. processing conditions, sugar content etc.), or may involve historical data (such as source, and storage or transportation conditions or events) or even somewhat subjective evaluation data such

as taste or texture, or apparently unconnected data, such as food color or appearance. In addition, the distribution itself may include information that is outside the range of conventional microbiological testing, such as test results for marker species associated with food-specific taste or texture factors, or associated with environmental niches that are known to support additional organisms that are not themselves tested (or with organisms for which no direct test exists).

Because the distribution is a multi-dimensional output, it has the power to resolve (i.e., it changes in response to variations in) numerous other data parameters, and according to further aspects of the invention these associations are discovered by simply building a database and applying correlation and database processing techniques.

Thus, applicant's testing with a species array to produce a distribution is believed to be a substantial departure from the cited art, wherein, although genomic testing and hybridization probe methodology are used for microbiological tests, this has been done simply to test for more organisms, or perform more tests for one organism. Applicant, by contrast, produces a multidimensional distribution output, and the enhanced information content of the distribution, in turn, is used in further embodiments of the method to determine not simply whether the food product is good or bad, but to effectively define measures along multiple axes, and to discover or identify correlated effects, e.g., to judge whether a harvested component was susceptible, whether a process pH may have been variant, whether taste is likely to be affected and to detect other food history or process parameter factors (for example, by correlating these with prior food and test records). According to various aspects of these further features set forth in the dependent claims, the method includes establishing a database and performing data mining or correlation of distributions against the database.

Thus, rather than simply testing a sample for the presence of a suspected organism, or any of a plurality of organisms (as is done for various clinical health or water supply applications), applicant assays for multiple different sequences of plural different species and produces a distribution, a multi-dimensional output. As set forth in various ones of the

dependent claims discussed below, applicant's methodology further applies this multi-dimensional output to produce databases and derived data that extends far beyond the simple observation of the presence or characterization of a contaminant or pathogen taught by the references. Conceptually, as described in the disclosure, the various species may be selected to correspond to multiple dimensions of the sample- it's history, condition etc. as well as testing for actual pathogens. However, even without conscious selection of species known to indicate specific conditions, history or processing result, the multi-dimensionality of the distribution is expected to allow the processing to reveal (by mining and correlation or construction of relational databases) such associations with conditions.

The distinctions between applicant's invention and the prior art will be better understood in view of the following discussion of the cited art.

United States Patent 6,057,100 of Heyneker shows an oligonucleotide array comprised of a plurality of stripes or fibers, wherein each stripe has one probe, i.e., one oligonucleotide species, attached to it (column 5, line10-11). The fibers can be woven into a sheet, with all the woof (or else all of the weft) fibers so treated, so that either the horizontal or the vertical stripes are sensitized to bind to specific target genomic sequences. The sheets can then be cut cross-wise to provide a multi-oligonucleotide band, which is formed of short, parallel cross-segments that each test for one oligonucleotide. Furthermore, one of these bands may be attached to a support with other similarly-fabricated bands to form an array. These arrays may be used to test for multiple oligonucleotides. For example, the '100 patent suggests that such arrays be employed to more reliably detect HIV virus (which mutates quickly) by employing nucleotides directed to many "highly conserved HIV sequences" (column 8, lines 60-65). In effect, the array would be fabricated to detect the genome of a single organism or species. Many oligonucleotides would also be used for a task such as cDNA testing (column 3, lines 7-9). The patent also states that "nucleic acids of the invention (may) find use as probes for toxic bacteria in the screening of water and food samples" using "oligonucleotides designed to recognize bacterial strains" (column 9, lines 5-12).

Thus, the Heyneker patent contemplates detecting an elusive virus by providing multiple hybridization stripes, each with a different oligonucleotide probe for the HIV virus, thus enhancing the likelihood of responding to presence of the virus. It suggests this approach because the HIV virus mutates quickly, and thus the prospects of detection are enhanced if the probe is able to test for many different highly conserved (e.g., non-mutating) regions. Heyneker also contemplates applying the arrays to detect one or more clinical or food pathogens.

It appears that Heyneker's basic technology could be used to construct arrays for application in applicant's methods. However, Heyneker's basic concept is that single-oligonucleotide stripes may be more efficiently treated with the small quantities of available probe material, and will provide a more efficiently visible or detectable locus than a conventional dot-like hybridization region, and also allow multi-point averaging of signal values along the stripe. These stripes are then attached to a support surface. Heyneker distinguishes his invention from the prior art wherein many different probes must be built up on, requiring use of relatively short probe sequences, or must be microdispensed onto a single support surface, resulting in relatively variable response characteristics. Notably, however, the cited patent teaches attaching only a single oligonucleotide to each stripe, and except for cases such as the HIV virus or human cDNA analysis, does not appear to teach employing multiple probe oligonucleotides for a single organism or species. It's teaching of an array that detects multiple different species is illustrated simply as detecting "the presence or absence" of known pathogens (column 1, lines 58-64). There is no mention of producing a distribution as described by applicant, or of systems that process or store distributions.

Heyneker does not show or teach detecting plural different sequences from a plurality of different organisms to produce a distribution output, and only with the application of hindsight would one (impermissibly) read Heyneker as teaching a test that produces a distribution output as claimed by applicant. Furthermore, there is no teaching of the further inventions set forth in applicant's dependent claims, of storing distributions with other types of data, and employing

relational databases, correlation techniques or data mining to identify danger conditions or food-related parameters of interest.

Reading the Heyneker patent, it is clear that it does not remotely suggest a method in which the array has been configured, and the procedure is carried out to produce a distribution output as claimed by applicant. Furthermore, Heyneker has no suggestion that a set of test results constitute a distribution constituting an object or data set in its own right, providing a multi-dimensional indication of the original sample. The Heyneker patent has no suggestion of any steps to select a set of oligonucleotides and probes such that they will not have cross-reactivities (or alternatively to characterize their cross reactivities), nor does it deal with the problem of preparing a complex sample, such as a food or environmental sample, so that many of the target organisms or sequences may be cultured or amplified for detection, if present. It does not suggest determining sensitivities, or calibration as discussed in applicant's disclosure. The Heyneker patent, to the extent it deals with sample preparation, simply assumes that samples will be "treated as is known in the art, including any sample preparation such as purification or amplification" (column 9, lines 22-25). Further, Heyneker is entirely silent as to applicants methods of forming and mining a database .

Thus, Heyneker is properly characterized as simply describing an improved technology for forming arrays that carry out multiple tests, with the active hybridization sites formed of strips or shorter segments, which may employ the same or different oligomers in different embodiments.

The subsidiary references cited in the Office Action show various multi-bacteria probes and automated fluidics systems for automating sample preparation steps. Of these, the Bergeron et al '564 patent is perhaps most relevant, as it teaches probe arrays that are specifically designed to test for multiple pathogens, and to detect specific sequences so as to identify, for example, antibiotic-resistant organisms. However, reading that patent as a whole, it is clear that it is directed to enhancing the speed and inclusiveness of testing for bacteria. It does not suggest

the output of distributions, or the building of relational or mineable distribution databases and their use in identifying extrinsic conditions such as process or food history or other parameters as claimed by applicant.

Accordingly the cited art neither show nor collectively suggests the invention now set forth in applicant's independent claims, and the previously asserted rejections have no application to the amended claims. All claims are therefore now allowable, and the dependent claims are each also allowable for the further reasons adduced above.

For all of the above reasons, applicant respectfully requests that the Examiner reconsider the application, approve the formal drawings submitted herewith, examine the claims, and allow all claims at this time.

In the event that the Examiner considers that any other matter requires attention before allowance, the Examiner is urged to telephone the undersigned to address such matter or schedule an interview so as to expedite further prosecution of the application.

Respectfully submitted,

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MARKED-UP COPY OF CLAIMS SHOWING CHANGES

Claims

1.(Once Amended) A method of food product testing, such method including the steps of

taking a sample of a food product and preparing [a food] the sample [and ,] for assay of genomic material from a plurality of target species potentially present in the food product, and

[simultaneously detecting genomic material from a plurality of species with] contacting the prepared food sample with an array of probes [to form] directed to multiple regions of genomic material for each of a plurality of said target species

such that said material hybridizes at loci of said array, to simultaneously detect genomic material from a plurality of said target species, and

forming an output distribution of the species in the food sample.

2. (Once Amended) The method of claim 1, wherein the step of preparing includes the step of culturing the food sample to increase populations of a plurality of the target [organisms] species prior to testing with the array of probes.

7. (Once Amended) The method of claim 6, further wherein a computer operates upon an output of an array reader to output said distribution, and including the steps of storing an output distribution in a database together with data regarding the food sample from which the distribution is derived, and operating a data mining program effective to correlate a detected distribution with stored database information.

8. (Once Amended) The method of claim 1, [comprising] wherein the step of preparing the sample includes the steps of recovering [plural] a plurality of different microorganisms from the food sample, extracting DNA from the plural different microorganisms, and simultaneously amplifying plural target sequences present in the recovered DNA for each of said different microorganisms.

9. (Once Amended) The method of claim 1, further comprising the step of correlating the output distribution with a database [including] wherein the database includes data of at least one type selected from among [of]

(i) other output distributions,

(ii) [food] parameters related to the source, condition or processing of food in the sample from which the ouput distribution was taken, and [process history]

(iii) parameters related to the source, condition or processing of food in the sample from which other ouput distributions were taken.

Claims 10 – 13 are canceled.

14.(Once Amended) A testing method comprising the steps of

preparing an array having plurality of probes directed to target sequences of each of a defined plurality of different target species

preparing a sample, wherein the step of preparing a sample includes extracting DNA from the sample, including sequences of the [defined] species present in the sample,.

treating the extracted DNA with a PCR protocol effective to preferentially and simultaneously increase the level of target DNA sequences of the defined plurality of different target species, and

hybridizing the amplified DNA to the probes on the array [to thereby determine] and forming an output distribution representative of the target species present in the sample.

18. (Once Amended)The testing method of claim 14, wherein the target sequences include species sequences coding for factors involved in pathogenesis [pathogenicity] or virulence factors.

Claim 22 is canceled

NEW CLAIMS:

23. The testing method of claim 14, wherein the target sequences are species sequences selected for efficient probe hybridization and detection as a group.

24. The testing method of claim 14, further including the steps of determining sensitivity and cross reactivity of the array.

25. The testing method of claim 14, wherein the output distribution indicates amount of each target species present in the sample.

MARKED_UP COPY OF ABSTRACT SHOWING CHANGES

Abstract

A testing system useful for food products employs a multispecies testing array to test for presence or amount of a plurality of organisms in a sample by detecting plural characteristic sequences for each of plural organisms [. A data processing module reads the array] to form a multispecies distribution output or microbial profile, and this is processed or used in conjunction with data mining to provide trend, warning or other data. [Using look-up or correlation, preferably in conjunction with data mining, the processing module produces] The processor correlates and stores information relating to taste, smell, texture, processing conditions, quality or source of a component or ingredient, potential pathogenicity or other factor [. A single test thus provides quantitative and qualitative information about entire populations of microbial species in a tested sample, and the utility of the output distribution adds significant value to microbial testing. Correlation between microbial profiles and ingredient quality, flavor potential, and the likelihood of carrying otherwise undetectable or difficult to detect organisms allow process parameters to be changed or improved to address the identified conditions. The system provides] , with correlations on a multidimensional space yielding new preconditions or warning indications, and [provides] providing a mechanism for specialization of the species distribution data for specific products, as well as for incorporation or development of process changes and company trade secrets. [The array testing and processing sequence may involve culture multiplication, nucleic acid extraction, PCR amplification, labeling of targets and hybridization to the probe matrix array, followed by fluorescence detection and image analysis, to provide information on the presence and/or distribution of a specific group of organisms. The system is readily adapted to include new or proprietary DNA probes, assays or markers that are specific to the organisms, processes and materials of interest. The arrays may be configured with different species and gene sequences to effect clinical or diagnostic testing, workplace or environmental testing, and may be applied to other situations in which the determination of multispecies distributions solves for a diagnostic, corrective or analytic intervention.]